**Application No.:** 10/560,485

Office Action Dated: October 27, 2008

This listing of claims will replace all prior versions, and listings, of claims in the application.

**PATENT** 

## **Listing of Claims:**

## 1. (Original) A compound of formula (I)

$$L-N \longrightarrow CH_2-N-C \longrightarrow R^4$$

$$R^3 \quad (I),$$

$$R^1 \qquad R^2$$

a stereochemically isomeric form thereof, an N-oxide form thereof, or a pharmaceutically acceptable acid or base addition salt thereof, wherein

-R<sup>1</sup>-R<sup>2</sup>- is a bivalent radical of formula

$$-O-CH_2-O-$$
 (a-1),

$$-O-CH_2-CH_2-$$
 (a-2),

$$-O-CH_2-CH_2-O-$$
 (a-3),

$$-O-CH_2-CH_2-CH_2-$$
 (a-4),

$$-O-CH_2-CH_2-CH_2-O-$$
 (a-5),

$$-O-CH_2-CH_2-CH_2-$$
 (a-6),

$$-O-CH_2-CH_2-CH_2-CH_2-O-$$
 (a-7),

wherein in said bivalent radicals optionally one or two hydrogen atoms on the same or a different carbon atom may be replaced by  $C_{1-6}$ alkyl or hydroxy,

 $R^3$  is  $C_{1-6}$ alkyl,  $C_{1-6}$ alkyloxy, or halo;

R<sup>4</sup> is hydrogen or halo;

provided that when  $R^3$  and  $R^4$  are both halo, then the bivalent radical- $R^1$ - $R^2$ - is of formula (a-5);

 $R^5$  is hydrogen or  $C_{1-6}$ alkyl, and the -OR<sup>5</sup> radical is situated at the 3- or 4-position of the piperidine moiety;

L is hydrogen, or L is a radical of formula

$$-Alk-R6 (b-1),$$

$$-Alk-X-R7 (b-2),$$

-Alk-Y-C(
$$=$$
O)-R<sup>9</sup> (b-3), or

wherein each Alk is  $C_{1-12}$ alkanediyl; and

**Application No.:** 10/560,485

Office Action Dated: October 27, 2008

R<sup>6</sup> is hydrogen; hydroxy; cyano; C<sub>3-6</sub>cycloalkyl; C<sub>1-6</sub>alkylsulfonylamino; aryl or Het;

 $R^7$  is  $C_{1-6}$ alkyl;  $C_{1-6}$ alkyl substituted with hydroxy;  $C_{3-6}$ cycloalkyl; aryl or Het;

X is O, S, SO<sub>2</sub> or NR<sup>8</sup>; said R<sup>8</sup> being hydrogen or  $C_{1-6}$ alkyl;

 $R^9$  is hydrogen,  $C_{1-6}$ alkyl,  $C_{3-6}$ cycloalkyl, hydroxy or aryl;

Y is a direct bond, or NR<sup>10</sup> wherein R<sup>10</sup> is hydrogen or  $C_{1-6}$ alkyl;

Z is a direct bond, O, S, or  $NR^{10}$  wherein  $R^{10}$  is hydrogen or  $C_{1-6}$ alkyl;

 $R^{11}$  and  $R^{12}$  each independently are hydrogen,  $C_{1\text{-}6}$ alkyl,  $C_{3\text{-}6}$ cycloalkyl, or  $R^{11}$  and  $R^{12}$  combined with the nitrogen atom bearing  $R^{11}$  and  $R^{12}$  may form a pyrrolidinyl, piperidinyl, piperazinyl or 4-morpholinyl ring both being optionally substituted with  $C_{1\text{-}6}$ alkyl;

aryl represents unsubstituted phenyl or phenyl substituted with 1, 2 or 3 substituents each independently selected from halo, hydroxy,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkyloxy,

 $C_{1\text{-}6}$ alkylcarbonyl, nitro, trifluoromethyl, amino, aminocarbonyl, and aminosulfonyl; and

Het is furanyl; furanyl substituted with  $C_{1-6}$ alkyl or halo;

tetrahydrofuranyl; tetrahydrofuranyl substituted with C<sub>1-6</sub>alkyl;

dioxolanyl; dioxolanyl substituted with C<sub>1-6</sub>alkyl;

dioxanyl; dioxanyl substituted with  $C_{1-6}$ alkyl;

tetrahydropyranyl; tetrahydropyranyl substituted with C<sub>1-6</sub>alkyl;

2,3-dihydro-2-oxo-1H-imidazolyl; 2,3-dihydro-2-oxo-1H-imidazolyl substituted with one or two substituents each independently selected from halo, or  $C_{1-6}$ alkyl; pyrrolidinyl; pyrrolidinyl substituted with one or two substituents each

independently selected from halo, hydroxy, or  $C_{1-6}$ alkyl;

pyridinyl; pyridinyl substituted with one or two substituents each independently selected from halo, hydroxy,  $C_{1-6}$ alkyl;

pyrimidinyl; pyrimidinyl substituted with one or two substituents each independently selected from halo, hydroxy, or  $C_{1-6}$ alkyl;

pyridazinyl; pyridazinyl substituted with one or two substituents each independently selected from hydroxy,  $C_{1\text{-}6}$ alkyloxy,  $C_{1\text{-}6}$ alkyl or halo; pyrazinyl; pyrazinyl substituted with one ore two substituents each independently selected from hydroxy,  $C_{1\text{-}6}$ alkyloxy,  $C_{1\text{-}6}$ alkyl or halo.

2. (Previously Presented) The compound as claimed in claim 1 wherein the –OR<sup>5</sup> radical is situated at the 3-position of the piperidine moiety having the trans configuration.

**Application No.:** 10/560,485

Office Action Dated: October 27, 2008

3. (Previously Presented) The compound as claimed in claim 2 wherein the absolute configuration of said piperidine moiety is (3S, 4S).

4. (Previously Presented) The compound as claimed in claim 1 wherein -R<sup>1</sup>-R<sup>2</sup>- is a radical of formula (a-5), R<sup>3</sup> is chloro and R<sup>4</sup> is chloro.

**PATENT** 

- 5. (Previously Presented) The compound as claimed in claim 1 wherein -R<sup>1</sup>-R<sup>2</sup>- is a radical of formula (a-5), R<sup>3</sup> is chloro and R<sup>4</sup> is bromo.
- 6. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically active amount of a compound according to claim 1.
- 7. (Canceled)
- 8. (Canceled)
- 9. (Withdrawn) A compound of formula (III)

$$R^4$$
 $R^3$ 
 $R^1$ 
 $R^2$ 
(III)

wherein

-R<sup>1</sup>-R<sup>2</sup>- is a bivalent radical of formula

$$-O-CH_2-CH_2-CH_2-O-$$
 (a-5),

wherein in said bivalent radicals optionally one or two hydrogen atoms on the same or a different carbon atom may be replaced by  $C_{1-6}$ alkyl or hydroxy;

 $R^3$  is  $C_{1-6}$ alkyl,  $C_{1-6}$ alkyloxy, or halo; and

R<sup>4</sup> is hydrogen or halo.

- 10. (Original) A process for preparing a compound of formula (I) wherein
  - a) an intermediate of formula (II) is reacted with an carboxylic acid derivative of formula (III) or a reactive functional derivative thereof;

**Application No.:** 10/560,485

Office Action Dated: October 27, 2008

$$L = N + HO = C + R^{4}$$

$$(II)$$

$$(III)$$

$$(III)$$

$$(III)$$

b) an intermediate of formula (IV) is *N*-alkylated with a compound of formula (I-a), defined as a compound of formula (I) wherein L represents hydrogen, in a reaction-inert solvent and, optionally in the presence of a suitable base, thereby yielding compounds of formula (I-b), defined as compounds of formula (I) wherein L is other than hydrogen;

c) an appropriate ketone or aldehyde intermediate of formula L'=O (V), said L'=O being a compound of formula L-H, wherein two geminal hydrogen atoms in the C<sub>1-12</sub>alkanediyl moiety are replaced by =O, is reacted with a compound of formula (I-a), thereby yielding compounds of formula (I-b);

$$L = O + H - N \longrightarrow CH_2 - N - C \longrightarrow R^4$$

$$(I-a) \qquad R^1 \longrightarrow R^2$$
(I-b)

wherein in the above reaction schemes the radicals -R<sup>1</sup>-R<sup>2</sup>-, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are as defined in claim 1 and W is an appropriate leaving group;

d) or, compounds of formula (I) are converted into each other following art-known transformation reactions; or if desired; a compound of formula (I) is converted into a pharmaceutically acceptable acid addition salt, or conversely, an acid addition salt of a compound of formula (I) is converted into a free base form with alkali; and, if desired, preparing stereochemically isomeric forms thereof.

**Application No.:** 10/560,485

Office Action Dated: October 27, 2008

11. (Withdrawn) A method for the treatment of 5HT<sub>4</sub> related disorders comprising administering to a patient in need thereof an effective amount of a compound according to claim 1.

**PATENT** 

- 12. (Withdrawn) A method for treating patients suffering from gastrointestinal conditions comprising administering to the patient an effective amount of a compound according to claim 1.
- 13. (Withdrawn) A method for treating hypermotility, irritable bowel syndrome, constipation or diarrhea predominant IDS, pain and non-pain predominant IBS and bowel hypersensitivity comprising administering to a patient in need thereof an effective amount of a compound according to claim 1.